REMARKS

Response to Restriction Requirement

In response to the Examiner's restriction of the claims, Applicants hereby provisionally elect, with traverse, Invention II (claims 5-10, 16-21 and 23), drawn to a non-human transgenic animal comprising a disruption in a secreted protein gene, cells comprising a disruption in a secreted protein gene, and methods of making the transgenic non-human animal comprising a disruption in a secreted protein gene using the cells, and *in vivo* methods of using the animals to identify an agent that modulates the expression of a secreted protein gene.

In the restriction, the Examiner asserts that claims 1-35 are drawn to twelve distinct subjects, grouped as: Invention I (claims 1-4), drawn to a targeting construct and a method of producing the gene-targeting construct, classified in class 536, subclass 23.1; Invention II (claims 5-10, 16-21 and 23), drawn to a non-human transgenic animal comprising a disruption in a secreted protein gene, cells comprising a disruption in a secreted protein gene, and methods of making the transgenic non-human animal comprising a disruption in a secreted protein gene using the cells, and *in vivo* methods of using the animals to identify an agent that modulates the expression of a secreted protein gene, classified in class 800, subclasses 3, 8, 21, and 25 and class 435, subclasses 455, 463, 320.1, and 325 and class 424, subclass 9.2; Invention III (claims 11 and 12), drawn to an *in vivo* method of identifying an agent that modulates a secreted protein gene, classified in class 800, subclass 3; Invention IV (claims 13 and 14), drawn to an *in vitro* method of identifying an agent that modulates the expression of a secreted protein encoding gene using a cell comprising a disruption in a secreted protein gene, classified in class 435, subclasses 4 and 6; Invention V (claim 15), drawn to an unknown agent that modulates the expression of a secreted protein encoding gene using a non-human transgenic animal, not classified; Invention VI (claim 22), drawn to methods of identifying agents that modulate expression of a secreted protein gene using a transgenic mouse comprising a disruption in a secreted protein gene, classified in class 800, subclass 3; Invention VII (claims 24 and 25), drawn to methods of identifying an agent that modulates the function of a secreted protein gene using a cell comprising a secreted protein gene, classified in class 435 subclass 6; Invention VIII (claim 26), drawn to an *in vitro* method of identifying an agent that has an effect on depression using a secreted protein, classified in class 435, subclass 4; Invention IX (claim 27), drawn to an *in vitro* method of identifying an agent that

has an effect on depression using a cell expressing a secreted protein gene, classified in class 435, subclass 6; Invention X (claims 28 and 29), drawn to an *in vitro* method of identifying an agent that has an effect on depression using a cell over-expressing a secreted protein gene, classified in class 435, subclass 6; Invention XI (claim 30), drawn to an unknown agent that has an effect on depression, not classified; and Invention XII (claims 31-35), drawn to a method of treating depression in a patient by administering an agent, classified in class 514, subclass 2.

The instant Office Action generally asserts that restriction is warranted between the invention groups in that the claimed inventions are patentably distinct. The Examiner has based this conclusion on several factors, including that the inventions are allegedly mutually exclusive and independent, are used independently of each other, are practiced with materially different process steps and technical considerations, or require materially distinct protocols and reagents. Applicants disagree with the Examiner's conclusions. Applicants respectfully traverse the requirement for restriction and request reconsideration and withdrawal of the requirement.

Specifically, the Examiner asserts that the claims of Invention I and Invention II are patentably distinct in that the nucleic acid construct of Invention I can be used as a probe while the cells of Invention I can be used in *in vitro* assays, and the transgenic non-human animal of Invention II can be used to observe a secreted protein gene function or as a model for disease or condition. Applicants disagree with the Examiner's conclusion in that the subject matter of Inventions I and II are closely related. More particularly, the targeting construct of Invention I and the transgenic animal of Invention II relate to disruption of the target secreted protein gene and determination of the function of the gene. A search or examination on the subject matter of both Inventions would not place undue burden on the Examiner.

The Examiner also asserts that the claims of Invention I and any of Inventions III–XII are patentably distinct in that the inventions are mutually exclusive and independent. The Examiner uses the example that the nucleic acid construct of Invention I is not required for implementing the *in vivo* and *in vitro* methods of Inventions III-XII. Applicants disagree with the Examiner's conclusion in that the inventions are related. A search or examination of the prior art on these inventions together would not put an undue burden on the Examiner.

The Examiner further asserts that the claims of Invention II and each of Inventions III, IV and VI are related as product and process of use. However, the Examiner states that the inventions are patentably distinct in that the subject matter of Invention II can be used in materially different

processes than those recited in the claims of Inventions III, IV and VI. The Examiner uses the example of using the transgenic non-human animal as a model for disease or the cells of Invention II to produce a secreted protein *in vitro*. Applicants disagree with the Examiner's conclusion and dispute the examples cited. In particular, Applicants do not believe that the Examiner has presented reasonable examples of how the cells and animals of Invention II could be used in materially different processes. For example, Applicants submit that the cells of Invention III could not be used as suggested by the Examiner in that the cells comprise a disruption in the secreted protein gene. Applicants submit that the cells and animals of Invention II and the methods of identifying agents are closely related.

The Examiner also asserts that the claims of Inventions II and V are patentably distinct in that they are mutually exclusive and independent. In particular, the Examiner states that the transgenic non-human animals of Invention II are not required for the agent of Invention V, and the agent is not necessary for the transgenic non-human animals. Applicants disagree. Applicants submit that the two invention groups are both related to the depression related phenotype exhibited by the transgenic animals.

The Examiner further asserts that the claims of Invention II and any of Inventions VII-X and XII are patentably distinct in that the inventions do not require each other. Specifically, the Examiner states that the animals of Invention II are not necessary for the methods of any of Inventions VII-X and XII, and that the methods are not necessary for the transgenic non-human animals. Applicants do not believe that the Examiner has provided sufficient evidence to establish that the inventions are unrelated. In particular, Applicants submit that each of the inventions is related in that they recite the use of the secreted protein gene.

The Examiner asserts that the claims of Inventions II and XI are mutually exclusive and independent in that they do not require each other. Applicants disagree. Applicants submit that the inventions are closely related, and could be searched without undue burden to the Examiner.

In addition, the Examiner concludes that the claims of Invention III and each of Inventions IV, VI-X and XII are mutually exclusive and independent in that they do not require each other. Applicants disagree that the inventions are unrelated as a result of not requiring the other. Applicants submit that the inventions are closely related. In particular, the inventions each relate to identifying or using agents that would modulate the expression or activity of the secreted protein gene related to depression, and involve the same or similar steps and modes of operation.

The Examiner states that the claims of Inventions III, IV, VI-X or XII and Invention V are patentably distinct because the agent of Invention V can be identified using different methods than those of Inventions III, IV, VI-X or XII. Applicants disagree in that the inventions are closely related, specifically to identifying or using agents that modulate the secreted protein gene related to depression.

The Examiner further states that the claims of Inventions III, IV, VI-X or XII and Invention XI are patentably distinct because the agent of Invention XI can be identified using different methods. Applicants disagree, in that the claims of Inventions III, IV, VI-X, XII and XI are closely related and could be examined without undue burden.

The Examiner further asserts that the claims of Invention IV and each of Inventions VI-X or XII are mutually exclusive and independent. The Examiner states that each of the methods requires a separate and materially different protocol. Applicants disagree with the Examiner's conclusions regarding separate and materially different protocols. Applicants submit that the methods require the same or very similar protocols and steps, and similar modes of operation. For example, the methods of Inventions IV and VI require the steps of administering a putative agent to a transgenic mouse with a disruption in the secreted protein gene and monitoring the effect of the agent on the expression or function of the gene in the mouse. As such, the methods are clearly related. The Examiner further states that the methods of Invention IV and each of Inventions VI-X and XII are classified differently, however, Applicants note that several of these invention groups have the same classification. For example, the methods of each of Inventions IV, VII, IX and X were classified in 435, subclass 6, and several, if not most, of these invention groups were classified under class 435.

The Examiner also asserts that the claims of Inventions V and XI are patentably distinct because the protocols and reagents required for each agent and the methods are materially distinct and separate. Applicants disagree. Applicants submit that the agents have similar function and structure, were identified by the same or similar method steps and are clearly related.

The Examiner asserts that the claims of Invention VI and any of Inventions VII-X or XII are mutually exclusive and independent in that the methods require separate and materially different protocols. The Examiner provides several general statements that the methods do not require each other, but does not establish that the methods require different steps or modes of

operation. Applicants submit that the inventions are related in that they require the same or similar method steps and modes of operation.

The Examiner further states that the claims of Invention VII and any of Inventions VIII-X or XII are mutually exclusive and independent in that the methods require separate and materially different protocols. The Examiner provides general statements that the methods do not require each other, but does not establish that the methods require different steps or modes of operation or are unrelated. Applicants submit that the methods of Invention VII and Inventions VIII-X and XII are related in that they require the same or similar method steps and modes of operation.

Finally, the Examiner further concludes that the claims of Inventions VIII-X and XII are mutually different and plurally independent from each other because each is practiced with materially different process steps and technical considerations and requires materially distinct protocols and reagents. Applicants disagree in that the methods are closely related and would not require undue burden to search together.

As stated in MPEP §803, the requirements for a proper claim restriction are as follows: "(a) the inventions must be independent or distinct as claimed; and (b) there must be a serious burden on the examiner if restriction is required."

A proper claim restriction must place a "serious burden" on the Examiner if the claims were examined without a restriction. In order to establish a serious burden, the Examiner must "show by appropriate explanation one of the following: separate classification thereof, a separate status in the art, or a different field of search." This showing of a serious burden is required <u>even if the claimed inventions have been shown to be distinct</u>. See MPEP §808.02. (emphasis added).

Applicants submit that the Examiner has not established that a serious burden would result from a search of the invention groups together, which is required even when the invention groups have been shown to be patentably distinct. Applicants do not believe that the Examiner has fulfilled the requirements for a proper claim restriction based on a serious burden standard. Applicants believe that a search of any one of Invention groups I through XII would produce results that would encompass the subject matter of each of the twelve invention groups. For example, the claims of provisionally elected invention II relate to a transgenic non-human animal comprising a disruption in the secreted protein gene. Any search or examination of the prior art conducted on this subject matter, e.g. the secreted protein gene, or disruptions in this gene, would produce results related to each of the other invention groups, specifically including a targeting

construct targeting the secreted protein gene, methods of using the secreted protein or secreted protein gene disrupted mouse, and methods of using cells derived from the secreted protein gene disrupted mouse.. As a result, separate searches of the prior art would not be required. Thus, a serious burden would not be placed on the Examiner in order to conduct a search and examination of the claims of Inventions I through XII together.

Although Applicants have provisionally elected Invention II for the purposes of advancing prosecution of the present application, Applicants contend for the foregoing reasons that the requirement for restriction between Inventions I through XII is improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of the requirement.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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Date

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